TCF-3: A Wnt Pathway Effector and Nanog Regulator in Pluripotent Stem Cell Self-Renewal

Grant Award Details

TCF-3: A Wnt Pathway Effector and Nanog Regulator in Pluripotent Stem Cell Self-Renewal

Grant Type: Basic Biology II

Grant Number: RB2-01629

Project Objective: The goal of this project is to study the role of TCF3 in hESC growth and pluripotency by exploring the hypothesis that TCF3 acts as a transition switch for hESC exiting the pluripotent state.

Investigator:

Name:	Marian Waterman
Institution:	University of California, Irvine
Type:	PI

Human Stem Cell Use: Embryonic Stem Cell, iPS Cell

Cell Line Generation: iPS Cell

Award Value: $1,259,879

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: Year 4/NCE

View Report

Grant Application Details

Application Title: TCF-3: A Wnt Pathway Effector and Nanog Regulator in Pluripotent Stem Cell Self-Renewal

Public Abstract: Despite the enormous potential for human embryonic stem cells (hESCs) and human induced pluripotent stem cells (hiPSCs) for development of new treatments for human disease, there still remain important gaps in our knowledge about the molecular mechanisms regulating establishment and maintenance of the pluripotent state. Improved understanding of fundamental mechanisms regulating pluripotency could improve the ability to establish pluripotent stem cells, in understanding how to maintain them in the undifferentiated state and how to differentiate them into specific cell lineages. The research proposed here seeks to provide a fundamentally better understanding of pluripotency and how it is controlled in hES cells and closely related iPCs. Maintenance of stem cells is known to be controlled by a group of core proteins that keep them in an undifferentiated state. When these proteins are downregulated they undergo differentiation into specialized cell types. Little is known about how the master regulatory circuitry is regulated other than feedforward positive interaction between the three core regulatory factors. Here we propose to study another protein that interacts with these core regulatory proteins and that may be a key regulator of their activity. These studies can expand our definition of the core stem cell regulatory circuitry. Through the research proposed here we will obtain a better understanding of the molecular processes at work when pluripotent ES cells decide to commit to lineage specific differentiation. For example, what genes must be turned off or on to achieve differentiation into specific lineages? How do chromatin modifications contribute to this regulation? This could lead to improvements in culture of hES cells and in methods for making iPSCs. A better understanding of these features could help better control these cells for use in regenerative medicine. Because hES cells are derived from the human embryo, these studies will also contribute important insights into human embryonic pre-implantation development.

Statement of Benefit to California:	A primary goal of Proposition 71 is to translate basic stem cell research to clinical applications. The disability and loss of earning power and personal freedom resulting from a disease or disorder are devastating and create a financial burden for California in addition to the suffering caused to patients and their families. Therapies using human embryonic stem cells (hESCs) and the related induced pluripotent stem cells (hiPSCs) have the potential to change millions of lives. Using hESCs and hiPSCs as models of disease will help us understand the underlying causes of disease and likely aid in the development of drugs to treat those diseases. However, for the potential of these cells to be realized, we need a better understanding of how they can be grown and what factors regulate the growth and self-renewal of the stem cell population. Maintenance of stem cells in an undifferentiated state is still problematical and long term growth of stem cells can be associated with appearance of genetic alterations some of which have previously been associated with cancer development. Moreover, understanding the mechanisms regulating stem cell growth will be important not only in maintaining stem cells but also in understanding how to drive their differentiation into more specialized cells. Finally, understanding the factors that support stem cell growth will be important for understanding the risks of transplanting stem cells and their differentiated derivatives into patients. Therefore, the raison d'etre for the proposed research is to provide a fundamentally better understanding of how hESCs and hiPSCs grow and self-renew. Anticipated benefits of our research to the Citizens of California include: 1. Development of improved methods for growing pluripotent stem cells and developing new cell-based treatments for a variety of diseases and disorders. 2. Development of improved understanding the risks of transplantation of stem cell-derived cells into patients and therefore improving the safety of stem cell-based transplantation. 4. Improved methods for understanding normal development of the early embryo 6. Transfer of new technologies and intellectual property to the public realm with resulting IP revenues coming into the state 7. Creation of new biotechnology spin-off companies based on generated intellectual property 8. Creation of new jobs in the biotechnology sector. It is anticipated that, in the long term, the return to the State in terms of revenue, health benefits for its Citizens and job creation will be significant.